General

Guideline Title

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262).

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262). London (UK): National Institute for Health and Care Excellence (NICE); 2015 Feb. 70 p. (Technology appraisal guidance; no. 329).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Infliximab for subacute manifestations of ulcerative colitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Apr. 21 p. (Technology appraisal guidance; no. 140).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

- Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
  Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

- The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
- Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6 to 17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

- Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:
    - They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
    - They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Moderately to severely active ulcerative colitis

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy

Target Population

- Adult patients with moderately to severely active ulcerative colitis whose disease has responded inadequately to conventional therapy or who cannot tolerate, or have medical contraindications for, such therapies
- Children and young people aged 6 to 17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies

Interventions and Practices Considered

Infliximab, adalimumab and golimumab therapy

Major Outcomes Considered

- Clinical effectiveness
  - Mortality
  - Measures of disease activity
  - Rates of and duration of response, relapse and remission
  - Rates of hospitalisation
  - Rates of surgical intervention (both elective and emergency)
  - Time to surgical intervention (both elective and emergency)
  - Adverse events of treatment (including leakage and infections following surgery)
  - Health-related quality of life (HRQoL)
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare a Technology Assessment Report. The assessment report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Identification of Studies

A comprehensive search was undertaken to systematically identify literature relating to the clinical effectiveness and safety of infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis (UC) after the failure of conventional therapy. The search strategy comprised the following main elements:

- Searching of electronic databases
- Handsearching of bibliographies of retrieved papers, key journals and conference proceedings
- Contact with experts in the field

The following electronic databases were searched from inception for published trials and systematic reviews:

- MEDLINE, MEDLINE in-Process and Other Non-Indexed Citations: Ovid. 1946-December 2013
- EMBASE: Ovid. 1974 - December 2013
- Cochrane Library: Wiley Interscience
    - Cochrane Database of Systematic Reviews (CDSR). 1996-December 2013
    - Database of Abstracts of Reviews of Effects (DARE). 1995-December 2013
    - Cochrane Central Register of Controlled Trials (CCRT). 1995-December 2013
    - Cochrane Methodology Register. 1904-December 2013
    - Health Technology Assessment Database (HTA). 1995-December 2013
    - NHS Economic Evaluation Database (NHS EED). 1995-December 2013
- CINAHL: EBSCO. 1982-December 2013
- Web of Science Citation Index: Web of Knowledge. 1900-December 2013
- Conference Proceedings Citation Index: Web of Knowledge. 1990-December 2013
- BIOSIS Previews: Web of Knowledge. 1969-December 2013

The MEDLINE search strategy is presented in Appendix 2 of the assessment report. The search strategy combined freetext and MeSH (medical subject headings) or thesaurus terms relating to *ulcerative colitis*, with freetext and MeSH or thesaurus terms relating to *infliximab*, *adalimumab* or *golimumab* combined with highly sensitive filters to retrieve randomised controlled trials (RCTs) and systematic reviews. Search terms for infliximab biosimilars were also included. The search strategy was translated across all databases. No date or language restrictions were applied. Literature searches were conducted during December 2013. References were collected in a bibliographic management database and duplicates were removed.

Searches were undertaken to identify unpublished studies (nearing or at completion) relevant to the decision problem within the following research registers:

- Clinical Trials.gov (searched December 2013)
- UKCRN Portfolio database (searched December 2013)
- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) (searched March 2014)

Proceedings of the following conferences were searched from 2009-2014 (where possible) for recent research:

- Congress of Crohn's and Colitis Conference (ECCO)
- Digestive Disease Week (DDW)
- Gut (British Society of Gastroenterology)

Key journals were identified using the PubMed PubReMiner facility and electronic tables of contents were searched from March 2013 to February 2014 for the following journals:

- Inflammatory Bowel Diseases
- Alimentary Pharmacology & Therapeutics
- Gastroenterology
- Journal of Crohns & Colitis
- American Journal of Gastroenterology

Citation searches were performed on included studies in Web of Science in March 2014.

Manufacturers' submissions received by NICE, as well as any relevant systematic reviews, were also handsearched in order to identify any further potentially relevant clinical trials.

Inclusion and Exclusion Criteria

Study Selection

The selection of eligible articles was undertaken using a two-stage process. Firstly, in order to assess agreement in the sifting approach between systematic reviewers, a check for consistency was conducted in the early stages of the sifting process. The two reviewers double sifted a total of 940 titles and abstracts. Kappa statistics of 0.888 and 1.000 were obtained, indicating very high strength of agreement.

All remaining titles and abstracts were examined for inclusion by one reviewer (the reviewers each sifted 50% of total citations at title and abstract level). Any citations that clearly did not meet the inclusion criteria (e.g., animal studies, studies unrelated to UC) were excluded. During the second

stage of the sifting process, full text articles were examined for inclusion by one reviewer. Any uncertainty in the eligibility of potentially relevant full text articles was resolved through discussion. Trials retrieved for full paper screening which were subsequently excluded were tabulated (see Appendix 3 of the assessment report) together with justification for their exclusion.

Inclusion and Exclusion Criteria

See Section 5.1.2.2 of the assessment report for details of the inclusion criteria, including interventions, populations, comparators, outcomes, and study design. See Section 5.1.2.3 of the assessment report for details of the exclusion criteria.

Assessment of Cost-effectiveness

Identification of Studies

A comprehensive search was undertaken to systematically identify literature relating to the cost effectiveness of infliximab, adalimumab and golimumab for treating moderate-to-severe ulcerative colitis after the failure of conventional therapy. The search strategy comprised the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Handsearching of bibliographies of retrieved papers.

The following electronic databases were searched from inception for economic evaluations:

- MEDLINE, MEDLINE in-Process and Other Non-Indexed Citations: Ovid. 1946-present
- EMBASE: Ovid. 1974-2013
    - Cochrane Library: Wiley Interscience
    - Cochrane Database of Systematic Reviews (CDSR). 1996-present
    - Database of Abstracts of Reviews of Effects (DARE). 1995-present
    - Cochrane Central Register of Controlled Trials (CCRT). 1995-present
    - Cochrane Methodology Register. 1904-January 2014
    - Health Technology Assessment Database (HTA). 1995-present
- NHS Economic Evaluation Database (NHS EED). 1995-present
- CINAHL: EBSCO. 1982-present
- Web of Science Citation Index: Web of Knowledge. 1900-present
- Conference Proceedings Citation Index: Web of Knowledge. 1990-present
- BIOSIS Previews: Web of Knowledge. 1969-present
- EconLit: Ovid. 1886-present

The MEDLINE search strategy is presented in Appendix 10 of the assessment report. The search strategy combined freetext and MeSH or thesaurus terms relating to *ulcerative colitis*, with freetext and MeSH or thesaurus terms relating to *infliximab*, *adalimumab* and *golimumab* combined with highly sensitive economic filters to retrieve economic evaluations. The search strategy was translated across all databases. No date or language restrictions were applied. Literature searches were conducted during January 2014. References were collected in a bibliographic management database and duplicates were removed.

Inclusion and Exclusion Criteria

Studies were included in the systematic review if they reported full economic evaluations comparing infliximab, adalimumab and/or golimumab, against each other or against any other intervention, within their licensed indications for the treatment of patients with moderate to severe UC. The inclusion and exclusion criteria applied within the systematic review are presented in Box 1 of the assessment report. Studies were included only if they were reported as full papers; conference abstracts were excluded from the review as they present insufficient detail to allow for a rigorous assessment of study quality.

Review Methods

The results of the economic searches were sifted by title and abstract. The full papers of studies which potentially met the inclusion criteria were retrieved for further inspection. Studies included in the systematic review were critically appraised using the Drummond checklist for economic evaluations. In addition, the manufacturers of the products considered within this appraisal submitted economic evidence to NICE; these models were assessed against the NICE Reference Case. The structure and formulae included in the manufacturer's submission models were scrutinised by two members of the Assessment Group. It should be noted that this appraisal includes an update of Technology Appraisal Guidance 140; the

economic evaluation reported within the 2007 Schering Plough submission to NICE is not included in this review as it has previously been critiqued for NICE; however, one of the studies included in the review reports an analysis of this model.

Number of Source Documents

Assessment of Clinical Effectiveness

A total of ten randomised controlled trials (RCTs) were identified in the clinical effectiveness systematic review. Five, three and two RCTs evaluated the use of infliximab, adalimumab and golimumab respectively in the treatment of moderate to severely active ulcerative colitis (UC). Nine trials related to adults and one trial was conducted in a paediatric population. All of the adult RCTs (with the exception of one trial, UC-SUCCESS) were performed against placebo. No head-to-head RCTs were identified in which the interventions of interest were assessed against each other. See Figure 2 in the assessment report (see the "Availability of Companion Documents" field) for a flow diagram of study inclusion.

Assessment of Cost-effectiveness

- The systematic searches identified a total of 907 potentially relevant citations (see Table 34 and Figure 73 of the assessment report). In addition, 4 manufacturer's submissions were received by the National Institute for Health and Care Excellence (NICE). Two of the four submissions were submitted by the same manufacturer – one relating to golimumab and one relating to infliximab; as these relate to virtually identical models, they are considered as a single analysis within this assessment. Three of the included submissions to NICE included economic analyses; the submission from Celltrion did not include any economic analysis. Fourteen studies were excluded as they were available only in abstract form. A total of three published studies and three manufacturer's submissions reported economic analyses relating to the use of biologics for the treatment of moderate to severe ulcerative colitis.
- The Assessment Group developed a de novo economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare a Technology Assessment Report. The assessment report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Data Abstraction Strategy

Data relevant to the decision problem were extracted by one reviewer. Data were extracted without blinding to authors or journal. A data extraction form was developed and piloted on two included trials before slight revisions and final use on all included trials. Data relating to study arms in which the intervention treatments were administered in line with their licensed indications were extracted; data relating to the unlicensed use

of the interventions were not extracted. All extracted data were double-checked by a second reviewer. The safety data extracted were informed by the summary of product characteristics (SmPCs) for each product (available from http://www.medicines.org.uk/emc/). The key safety issues included such items as the number of patients experiencing infections, number of patients experiencing serious infections, number of patients experiencing malignancy, and the occurrences of infusion-related or injection-site reactions (as appropriate to the mode of administration for each intervention). Study results that were presented only in graphical format were digitised and estimated using Engauge software version 4.1. Where multiple publications of the same study were identified, data extraction was undertaken on all relevant associated publications, and findings were presented together with reference to their published source.

Critical Appraisal Strategy

The methodological quality of each included study was assessed by one reviewer. The quality of included studies was assessed using the Cochrane Risk of Bias Tool. This tool addresses specific domains, namely: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. Randomised controlled trials (RCTs) were classified as being at 'high risk' of attrition bias where drop-out in any treatment arm was ≥10%. The Assessment Group requested the trial protocols for all included trials from the manufacturers of the products included in this appraisal. These were received for some trials and were used, alongside Clinical Study Reports (CSRs) provided by the manufacturer for some trials and outcomes listed in ClinicalTrials.gov records, in order to inform the selective reporting domain of the Cochrane Risk of Bias tool. All quality assessment findings were double checked by a second reviewer.

Methods of Data Synthesis

The extracted data were presented for each study, both in structured tables and as a narrative description.

Methods for the Estimation of Efficacy Using Network Meta-analysis

Network meta-analysis methods are described in full alongside results in Section 5.2.3.3 of the assessment report.

Supplementary Meta-analyses

Where considered appropriate, secondary outcomes of interest were analysed using classical meta-analysis methods. Meta-analysis was undertaken using Cochrane Review Manager software (version 5.2). Outcomes reported as continuous data were estimated using a mean difference (MD) with 95% confidence intervals (95% CIs). Dichotomous outcomes were estimated as risk ratios (RRs) with associated 95% CIs. Where RCTs reported adverse events in sufficient detail, these were analysed as dichotomous data. Clinical heterogeneity across RCTs (the degree to which RCTs appear different in terms of participants, intervention type and duration and outcome type) was considered prior to data pooling. Random-effects models were applied. Effect estimates, estimated in Review Manager as Z-scores, were considered statistically significant at a cutoff of $p<0.05$.

See Section 5 of the assessment report for additional details on the evaluation of the clinical evidence.

Assessment of Cost-effectiveness

De novo Assessment Group Model

In light of the limitations of the models submitted by the manufacturers (see Section 6.1 of the assessment report), the Assessment Group developed a *de novo* health economic model to assess the cost-effectiveness of second-line infliximab, adalimumab and golimumab, conventional non-biologic therapies and immediate colectomy for the treatment of patients with moderate to severe ulcerative colitis (UC).

Model Scope

The scope of the economic analysis follows the NICE Reference Case (summarised in Box 4 of the assessment report).

The analysis compares infliximab, adalimumab and golimumab against each other and against conventional non-biologic therapy (comprised of a mix of 5-ASAs, immunosuppressants and corticosteroids) and immediate colectomy. Infliximab is assumed to be given at a dose of 5 mg/kg on three visits during induction and subsequently at a dose of 5 mg/kg every 8 weeks for patients who go on to receive maintenance therapy. Adalimumab is assumed to be given at one dose of 160 mg, one dose of 80 mg and two doses of 40 mg during the induction phase; a dose of 40 mg every other week (EOW) is assumed for patients who go on to receive maintenance therapy. A fixed proportion of adalimumab patients (27%) are assumed to escalate to a 40 mg every week (EW) dosing regimen, based on data reported in the AbbVie submission. Golimumab is assumed to be given as one dose of 200 mg and one dose of 100 mg during induction treatment, with subsequent maintenance therapy given at a dose of 100 mg every 4 weeks for patients with body mass greater than or equal to 80 kg or 50 mg every 4 weeks for patients with body mass less than 80 kg. Infliximab is assumed to be administered in a day case setting whilst the administration of golimumab and adalimumab is not assumed to

require any additional National Health Service (NHS) resources (no costs are included for training patients to self-inject). Patients in the non-surgical treatment groups are assumed to receive conventional background therapies (5-ASAs, immunosuppressants and corticosteroids). Surgery is included in the economic analysis both as a comparator within the analysis and also as a downstream component of the pathway for patients in the biologic and non-biologic treatment groups.

Model Structure

The Assessment Group model adopts a Markov structure with eight mutually exclusive health states (see Figure 88 of the assessment report). The model health states are defined according to whether the patient is alive or dead, the non-surgical treatment the patient is currently receiving (biologic therapy or non-biologic therapy), their prior history of colectomy and their current level of disease control (remission, response and active UC). Remission and response to treatment are classified according to the Mayo score, as defined within the trials included in the systematic review (see Chapter 5 of the assessment report). Remission is defined as a Mayo score ≤2 with no individual subscore >1. Response is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. As remission is a subset of the broader category of response, these are dealt with a mutually exclusive ordered categorical data (see Section 5.2.3.4 of the assessment report). Patients without either response or remission are defined as having active (moderate-to-severe) UC. The model includes the following health states: (1) on biologic treatment – active UC; (2) on biologic treatment – response; (3) on biologic treatment – remission; (4) on conventional treatment – active UC; (5) on conventional treatment – response; (6) on conventional treatment – remission; (7) post-surgery (with or without complications), and; (8) dead. Surgery is not included as a state but rather it is incorporated as an event; patients undergoing colectomy are assumed to transit to the post-surgery state if they survive their surgery and the dead state if they do not.

See Section 6 of the assessment report for further information on the analysis of economic evidence and details of the economic model.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the

basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on the Evidence for Cost-effectiveness

Availability and Nature of Evidence

The Committee concluded that all the models presented to it had shortcomings that inhibited the accurate estimation of the cost-effectiveness of tumour necrosis factor (TNF)-alpha inhibitors for ulcerative colitis.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee agreed that there was a high degree of uncertainty associated with the following aspects in the models:

- The assumptions about the sequencing and timing of conventional therapies in the pathway of care for ulcerative colitis
- The effectiveness of TNF-alpha inhibitors in patients in whom these agents are likely to be used in clinical practice; that is, patients with more severe disease who would start treatment at a younger age than patients in the trials
- The optimal duration of treatment with TNF-alpha inhibitors
- The long-term benefits of TNF-alpha inhibitors (that is, beyond the trial durations)
- The appropriate rate of surgery
- The benefit of TNF-alpha inhibitors in terms of avoiding or delaying surgery
- The cost of surgery and post-surgical care
- The utility values for patients at the different points in the pathway of care for ulcerative colitis, particularly for patients who had surgery
- The effect of TNF-alpha inhibitors on reducing corticosteroid use, with the associated long-term cost and health benefits.

It was also unclear to the Committee if and how all the above would differ for children and young people because much of the evidence did not relate to this population.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee was aware that it was particularly important to accurately capture the difference in utility between patients having TNF-alpha inhibitors and those who had surgery. It heard that several studies illustrated the poor quality of life of patients after surgery resulting from post-surgical complications. Furthermore, patients' responses to consultation suggested that quality of life after surgery is worse than that reported by one published study. The Committee concluded that this study is likely to have overestimated the utility value for patients who had surgery.

The Committee was not satisfied that the economic analysis had adequately captured all aspects of the patient's quality of life after surgery, particularly the emotional aspects and the long-term effects such as reduced fertility.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

There are no specific groups of people for whom the technology is particularly cost effective.

What Are the Key Drivers of Cost-effectiveness?

The Committee noted that the results of the Assessment Group's model were highly sensitive to the utility values used, specifically to the difference between the values for patients having medical treatment and those having surgery.

Most Likely Cost-effectiveness Estimate (Given as an Incremental Cost-effectiveness Ratio [ICER])

In the company's model for adalimumab, the base-case ICER for adalimumab compared with conventional therapy was £34,400 per quality-adjusted life year (QALY) gained. This was revised to £23,000 per QALY gained, a revision not critiqued by the Assessment Group. When the Assessment Group compared medical options only, infliximab was dominated by adalimumab, and golimumab was extendedly dominated by adalimumab and conventional therapy. The base-case ICER for adalimumab compared with conventional therapy was £50,600 per QALY gained.

For children and young people, the Assessment Group estimated an ICER of £68,400 per QALY gained for infliximab compared with conventional therapy. The Committee concluded that the economic analysis had tended to underestimate the cost effectiveness of TNF-alpha inhibitors.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the Technology Assessment Group (TAG). The main clinical effectiveness evidence came from randomised controlled trials. For cost-effectiveness, the Appraisal Committee considered economic models submitted by the manufacturers of the monoclonal antibodies and by the TAG.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Evidence was identified to demonstrate that patients receiving infliximab, adalimumab or golimumab were more likely to achieve clinical response and remission at induction and maintenance time points compared to patients receiving placebo.

Potential Harms

- The summary of product characteristics includes the following adverse reactions for adalimumab: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (including erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions.
- The summary of product characteristics includes the following adverse reactions for golimumab: upper respiratory tract infection and other

serious infections (including sepsis, pneumonia, tuberculosis, and invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematologic reactions.
- The summary of product characteristics includes the following adverse reactions for infliximab: upper respiratory tract infection, hepatitis B reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

- Contraindications to infliximab treatment include a history of hypersensitivity to infliximab or other murine proteins, the presence of tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections, and moderate or severe heart failure. Furthermore, women of childbearing potential must use adequate contraception and continue use for at least six months after last receipt of infliximab treatment.
- Contraindications to adalimumab treatment include hypersensitivity to the active substance, the presence of active tuberculosis or other severe infections such as sepsis, and opportunistic infections, and moderate to severe heart failure (New York Heart Association [NYHA] class III/IV). The administration of adalimumab during pregnancy is not recommended.
- Contraindications to golimumab include hypersensitivity to the active substance, the presence of active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections, and moderate or severe heart failure (NYHA class III/IV). The use of golimumab during pregnancy is not recommended.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has ulcerative colitis and the doctor responsible for their care thinks that infliximab, adalimumab or

golimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

- The Department of Health and Merck Sharp & Dohme have agreed that golimumab will be available to the NHS with a patient access scheme which makes the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Merck Sharp & Dohme Customer Service (01992 452094).
- NICE has developed a costing statement explaining the resource impact of this guidance.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262). London (UK): National Institute for Health and Care Excellence (NICE); 2015 Feb. 70 p. (Technology appraisal guidance; no. 329).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2008 Apr (revised 2015 Feb)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Infliximab for subacute manifestations of ulcerative colitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Apr. 21 p. (Technology appraisal guidance; no. 140).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Ulcerative colitis: implementing the NICE guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329). Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Feb. 12 p. (Technology appraisal guidance; no. 329). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Archer R, Tappenden P, Ren S, Martyn-St James M, Harvey R, Basirir H, Stevens J, Carroll C, Cantrell A, Lobo A, Hoque S. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model. Technology assessment report. Sheffield (UK): School of Health and Related Research (ScHARR), The University of Sheffield; 2014 Jun 24. 449 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Feb. 3 p. (Technology appraisal guidance; no. 329). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

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